DRUG EFFECTIVENESS REVIEW PROJECT

P&T Committee Brief
Drug Class Review on Beta$_2$-Agonists

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P & T COMMITTEE BRIEF
Inhaled Beta$_2$-Agonists: Comparative Drug Class Review Summary

Background:
Asthma is a chronic inflammatory disorder of the airways which causes recurrent episodes of wheezing, breathlessness, and cough associated with reversible airflow obstruction. It is estimated that 10.5% of the US population and up to 12% of Canadians have been diagnosed with asthma in their lifetime. There are two general classes of asthma medications: medications for long-term control and medications for the acute relief of airflow obstruction and symptoms. Long-term control medications include corticosteroids, cromolyn sodium and nedocromil, methylxanthines, leukotriene modifiers, and long-acting beta2-agonists (LABA). Medications for quick relief of bronchoconstriction and acute symptoms include short-acting beta2-agonists (SABA), anticholinergics and systemic corticosteroids. Exercise-Induced Asthma (EIA) is associated with airway obstruction after exercise. Pharmacologic therapy consists of an inhaled SABA 15 minutes prior to exercise. Additional daily therapy may be required to manage underlying chronic asthma.

Chronic Obstructive Pulmonary Disease (COPD) is a slowly progressive disease of the airways that is characterized by a gradual loss of lung function. The term COPD includes emphysema, chronic bronchitis, and chronic obstructive bronchitis. Cigarette smoking is linked causally to COPD in more than 80% of cases. In the U.S., an estimated 12.1 million adults were diagnosed with COPD in 2001, and in Canada, an estimated 3.7% of adults older than 35 years have the disease. COPD is the fourth leading cause of death in both countries. Since airflow obstruction is present in all persons with COPD, bronchodilators are a key part of therapy.

Inhaled beta2-agonists act primarily to relax airway smooth muscle. The LABA have a duration of at least 12 hours and are used for the long-term control of symptoms in moderate and severe persistent asthma, and for the prevention of EIA. They are not appropriate for the treatment of acute exacerbations. The SABA relax airway smooth muscle and increase airflow within 30 minutes and last 4 to 5 hours. They are the drug of choice for treating acute asthma symptoms and are used for preventing EIA. The SABA are not recommended for regularly scheduled, daily use.

Purpose:
This report examined the comparative effectiveness and safety of inhaled beta$_2$-agonists in treating asthma or COPD. The following drugs were considered:

LABA
- salmeterol (Serevent)
- formoterol (Foradil, Oxeze)

SABA
- albuterol (salbutamol in Canada) (Ventolin, Proventil, Accuneb)
- fenoterol (Berotec – only available in Canada)
- levalbuterol (Xopenex)
- metaproterenol (Alupent)
- pirbuterol (Exirel, Maxair)
- terbutaline (Bricanyl – only available in Canada)

Methodology:
The Drug Effectiveness Review Project reviewed all pertinent studies, and solicited and accepted public input. Literature searches for this review identified 6629 citations. Study eligibility was determined by pre-set criteria, which included study design and duration, patient population, interventions, and outcomes. Only head-to-head comparisons were included. Outcome measures included symptoms, quality of life, health care utilization, mortality and change in concurrent

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medication use. Studies published in a language other than English were excluded. The quality of all included studies was appraised.

Evidence Available:
Relevant information for this topic consists of 104 studies, including 84 for asthma, 6 for EIA and 14 for COPD. Most studies were of fair quality; nine were poor. The latter were included in the evidence tables, but did not contribute to the conclusions of the report.

Key Questions and Findings:
Question # 1. When used in adults with asthma or COPD, are there differences in efficacy or effectiveness among LABA, when used in the outpatient setting?

- In adults with asthma, four fair-quality studies found no differences between formoterol and salmeterol for the outcomes of symptoms, use of rescue medications, healthcare utilization, and quality of life.
- One small study examined EIA in adults, and found no significant difference between treatments in the fall of FEV_1, but a slower onset of bronchodilation with salmeterol and a greater increase in FEV_1 with formoterol.
- Two small studies compared effectiveness outcomes in patients with COPD, both finding no significant differences in symptoms in patients taking salmeterol and formoterol.

Question #2: When used in adults with asthma or COPD, are there differences in efficacy or effectiveness among the following SABA when used in the outpatient setting: albuterol, fenoterol, levalbuterol, metaproterenol, pirbuterol and terbutaline?

- In adults with asthma, a single trial examined albuterol or levalbuterol nebulizer treatments in the outpatient setting, and found both treatments decreased the mean number of puffs used per day of rescue medications (no between group statistics provided). The percentage of patients reporting “asthma” or “asthma increase” did not differ. In a second study, a greater percentage of patients given levalbuterol in the emergency department were discharged after 3 doses (no statistics provided). Hospitalization rates were similar for the two drugs, but the study was not powered to examine healthcare utilization. No studies that compared the effectiveness or safety of HFA propelled metered-dose inhaler(MDI) levalbuterol to albuterol were identified.
- In adults with asthma, five studies found no significant differences in effectiveness outcomes including the use of rescue medications and asthma symptom scores between albuterol and terbutaline. In contrast, one trial found mean asthma symptom scores were lower with terbutaline compared to albuterol.
- Among adults with asthma, two trials found no significant difference in symptom scores or patient preference between fenoterol and terbutaline.
- Among persons with COPD, only one head-to-head study compared fenoterol, terbutaline and albuterol. It reported drug preference (33% for fenoterol, 30% for albuterol and 25% for terbutaline), but provided no explanation of how this was measured, and between-group statistics were not given
- There were no studies identified in adults that included effectiveness outcomes for asthma, EIA or COPD for any of the following comparisons: albuterol vs. pirbuterol, albuterol vs. metaproterenol, metaproterenol vs. pirbuterol, metaproterenol vs. fenoterol, metaproterenol vs. terbutaline, pirbuterol vs. terbutaline.

Question #3: When used in children with asthma, are there differences in efficacy or effectiveness among LABA, when used in the outpatient setting?

- In children, one study evaluated effectiveness outcomes and found a higher discontinuation rate but better asthma severity score with formoterol compared to salmeterol. No significant difference was found for a number of other outcomes (frequency of poorly controlled days, frequency of mild exacerbations, percent experiencing a severe exacerbation, school attendance).

Question #4: When used in children with asthma, are there differences in efficacy or effectiveness among the following SABA when used in the outpatient setting: albuterol, fenoterol, levalbuterol, metaproterenol, pirbuterol and terbutaline?

- In children with asthma, symptoms and rescue medication use were not different between albuterol and levalbuterol , based on findings from four studies. Two of these evaluated outpatient regimens whereas the other two evaluated use in the emergency room (ER). In one of the outpatient studies, the only difference identified was a significantly greater improvement in asthma control days with levalbuterol 0.31 mg in the third week, compared to albuterol 1.25 mg and levalbuterol 0.63 mg. In a subgroup analysis of the other outpatient study, patients less than 33 pounds (15 kg) had more improvement in the Pediatric Asthma Caregiver's Quality of Life Questionnaire score with levalbuterol 0.63 mg than with albuterol. There were no differences in other outcomes. Findings from the two ER studies revealed no differences in any outcomes.
- Three studies examined health care utilization outcomes. Two smaller studies found no significant differences between albuterol and levalbuterol. The third study, which was powered to detect a difference, found a lower admission rate in the levalbuterol group. However, no difference in ER or hospital length of stay, or mean number of aerosols administered in the ER were found.
- In an exercise-challenge study of adolescents with EIA, albuterol and metaproterenol were equally efficacious in blocking exercise-induced bronchospasm initially. The duration of action of albuterol was significantly longer than for metaproterenol.
- In children with asthma, there was no significant difference between albuterol and terbutaline for symptoms, and respiratory rate decreased after both treatments.
- In a pediatric population with EIA, the only effectiveness outcome reported was the need for aminophyline treatment; 21% of patients receiving albuterol needed treatment compared to 8% of those treated with terbutaline.
- There were no studies identified in children that included effectiveness outcomes for asthma, EIA or COPD for any of the following comparisons: albuterol vs. pirbuterol, albuterol vs. fenoterol, metaproterenol vs. pirbuterol, metaproterenol vs. fenoterol, fenoterol vs. terbutaline, metaproterenol vs. terbutaline, pirbuterol vs. terbutaline.

Question #5: When used in adults with asthma or COPD, are there differences in safety or rates of adverse events among LABA when used in the outpatient setting?

- In adults, rates of total withdrawals and withdrawals due to adverse events from studies were similar between salmeterol and formoterol. There were no data on the comparative effect of these drugs on blood pressure, blood glucose, headache or tremor. The effect on heart rate was mixed, as was the frequency of palpitations and ventricular premature beats. One study found a greater decrease in potassium after formoterol compared to salmeterol.

Question #6: When used in adults with asthma or COPD, are there differences in safety or rates of adverse events among the following SABA when used in the outpatient setting: albuterol, fenoterol, levalbuterol, metaproterenol , pirbuterol and terbutaline?

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- In adults, four studies reported withdrawal rates, which were similar between levalbuterol and albuterol. Heart rate increased 5 to 15 beats per minute 20 minutes after treatment with both albuterol and levalbuterol, but returned to baseline by 3 hours. Between-group statistical comparisons were rarely reported. In the only study examining blood pressure, there were no significant changes in either group. Palpitations, tachycardia, light-headedness, dizziness, nervousness, anxiety, restlessness and tremor were reported in a similar percent of patients with both drugs. Blood glucose increased and potassium decreased after both drugs with no significant difference between the two drugs.
- No data on withdrawals were identified for albuterol vs. metaproterenol. Systolic blood pressure and heart rate increased in both drugs, with no significant difference between the drugs, although peak heart rate was greater with albuterol (one study). There were no comparative data on cardiovascular, metabolic, or neurologic adverse events.
- Rates of withdrawals were similarly low in both metaproterenol and pirbuterol treatment groups (one study). There were no comparative data on blood pressure or heart rate. A single study in an adult population found no significant differences in tachycardia, headache, dizziness, tremors, nausea or nervousness between the two groups.
- Rates of withdrawal were similar between albuterol vs. fenoterol. Between-group comparisons of blood pressure effects were not reported. Heart rate response was variable with both drugs. Palpitations were occasionally reported with both drugs with no difference between groups. A minor decrease in potassium was reported, with a greater decline with higher dosage of both drugs.
- Withdrawals were similar between albuterol and terbutaline. Effects on blood pressure were similar between the two drugs (one study). Heart rates generally increased, with similar changes after both drugs. Palpitations were noted in a small number of patients with both drugs. Potassium decreased, but no between-group p-values were reported (two studies).
- There were limited data on withdrawal rates for fenoterol compared to terbutaline, with only four studies reporting these data. In general, sample sizes were too small to draw conclusions. The available data on adverse events were sparse.
- No comparative data on withdrawals or cardiovascular, metabolic, or neurologic adverse events were provided in the included studies in adults for the following comparisons: albuterol vs. pirbuterol, metaproterenol vs. fenoterol, metaproterenol vs. terbutaline, and pirbuterol vs. terbutaline.

Question #7: When used in children with asthma, are there differences in safety or rates of adverse events among LABA, when used in the outpatient setting?

- In children, the single study reporting withdrawals found more participants taking formoterol at a dose not available in the U.S. withdrew than those taking salmeterol, due to deteriorating asthma control and adverse events.

Question #8: When used in children with asthma, are there differences in safety or rates of adverse events among the following SABA, when used in the outpatient setting: albuterol, fenoterol, levalbuterol, metaproterenol, pirbuterol and terbutaline?

- In children, study withdrawal rates comparing albuterol to levalbuterol in the two studies that reported these data were inconsistent.
- No comparative data on withdrawals or cardiovascular, metabolic, or neurologic adverse events were provided in the included studies in children for the following comparisons: albuterol vs. pirbuterol, albuterol vs. metaproterenol, albuterol vs. fenoterol, albuterol vs. terbutaline, metaproterenol vs. fenoterol, metaproterenol vs. terbutaline, pirbuterol vs. terbutaline, metaproterenol vs. pirbuterol, and fenoterol vs. terbutaline.

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Question #9: Are there subgroups of patients based on demographic characteristics, other medications, comorbidities, or pregnancy for which one LABA is more efficacious, effective, or associated with fewer adverse events than another?

- No study specifically examined a population greater than 65 years of age, although in several studies of COPD the mean population age was greater than 65 years. In trials of predominantly older men, a few outcomes were different between formoterol and salmeterol, but most outcomes did not differ.
- Only one study specifically examined comorbidities. Among 12 COPD patients with preexisting cardiac arrhythmias, there was a greater increase in heart rate and more supraventricular or ventricular premature beats after formoterol compared to salmeterol.

Question #10: Are there subgroups of patients based on demographic characteristics, other medications, co morbidities, or pregnancy for which one of the following SABA is more efficacious, effective, or associated with fewer adverse events: albuterol, levalbuterol, metaproterenol, pirbuterol, terbutaline, or fenoterol?

- No study specifically examined a population greater than 65 years of age, although in several studies of COPD the mean population age was greater than 65 years. The following comparisons found no significant differences in outcomes in trials that had primarily older or male populations: albuterol vs. levalbuterol, albuterol vs. metaproterenol, albuterol vs. pirbuterol, and metaproterenol vs. terbutaline.
- For the most part, race or ethnicity data were not provided in studies. Two studies compared albuterol to levalbuterol in predominantly African-American patients. In one, the hospitalization rate was significantly lower in levalbuterol compared to albuterol, while in the other, there were no significant differences between treatment groups for clinical asthma score and FEV1.

Conclusion:

For LABA, no significant differences were found between salmeterol and formoterol for any outcome studied in both adult asthma and COPD patients. In children, one study found no significant difference in most outcomes, but more improvement in parent-assessed quality of life, SABA use and some specific symptoms with formoterol. In adults with EIA, one study found a faster onset of action and a greater percent increase in FEV_1 prior to exercise with formoterol.

For SABA, no significant differences in symptoms were identified between albuterol and levalbuterol in adults, although one trial found a decrease in the need for additional treatment with levalbuterol in the outpatient setting, but no difference in hospital admission rates in the ER. For children, results were mixed for this comparison; some trials found no significant differences in outcomes, but one found more asthma control days in the outpatient setting, and another, fewer hospital admissions in the ER setting with levalbuterol. One trial found a longer duration of action for albuterol compared to metaproterenol in children with EIA. Limited effectiveness data found no significant differences for all other comparisons.

Consistent significant differences were not found for any adverse events for any comparisons. There were no consistent differences in effectiveness or adverse effects of any comparisons in any subpopulations.

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